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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,146	09/16/2002	Wilhelm Amberg	51748	9829

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

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05/16/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/089,146	AMBERG ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 7-10* is/are pending in the application.

4a) Of the above claim(s) *1-3 and 7-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 2/19/08, is acknowledged.

2. Claims 1-4 and 7-10 are pending.

3. Claims 1-3, 7-9 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

4. Claims 4 and 10 are under consideration in the instant application as they read on an a pharmaceutical composition for the treatment or prevention of cardiovascular diseases comprising an ETA endothelin blocker and an αvβ3 integrin receptor antagonist and a trade package thereof.

5. In view of the amendment filed on 2/19/08, only the following rejections are remained.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claim 4 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Kirchengast *et al* in view of Srivatsa *et al* (all of record) for the same reasons set forth in the previous Office Action mailed 9/21/07.

8. Claim 10 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Kirchengast *et al* in view of Srivatsa *et al* as applied to claim 4 above, and further in view of US Pat. No. 4,761,406 (all of record) for the same reasons set forth in the previous Office Action mailed 9/21/07.

Applicant's arguments, filed 2/19/08, have been fully considered, but have not been found convincing.

Applicant's arguments are summarized in that it is improper to simply dismiss the synergistic effect of the combination. Applicant submits that the application demonstrates that the pig coronary restenosis models "show that the combination of ET receptor antagonists and αvβ3 integrin receptor antagonists represents a more effective means of preventing restenosis than treatment with either drug alone." (emphasis added by Applicant) (page 17, line 44 to page 18, line2). Applicant submits that the application also demonstrates that side effects from combination therapy are less than those from separate treatment with each component. Applicant concludes that such results amount to synergistic and surprising effects of the claimed combination. Applicants assert that they rebutted the prima facie case with results that demonstrated synergistic and surprising effects of the combination.

It is the Examiner's position that the combination of ET_A endothelin blocker and αvβ3 integrin receptor antagonists would be expected to result in a more effective means of preventing restenosis than treatment with either drug alone. This is expected and does not mount to synergistic and surprising effects of the combination. Evidence of unexpected results must be weighed against evidence supporting prima facie obviousness in making a final determination of the obviousness of the claimed invention (MPEP 716.02(c). However, there is no data presented in the instant application to show a more effective means of preventing restenosis that treatment with either drug alone. No synergy has been shown with by using the claimed combination. Mere conclusions in the specification that the claimed combination had an unexpectedly a more effective means of preventing restenosis than treatment with either drug alone are not entitled to the weight of conclusions accompanying the statistical data or evidence in a declaration. See MPEP 716.02(a)-(c).

It is still the Examiner's position that the combined reference teachings arrived to the claimed invention. Once a *prima facie* case of obviousness has been made the burden of going further is shifted to applicant. *In re Keller*, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981). The evidence relied up should establish "that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance." *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). The Examiner points to the MPEP 716.02 which states that "evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness". There is no evidence in the instant specification that the combination of the claimed products described in the instant claims would differ in an unexpected manner from those described in the references. In the absence of unexpected results for the specific ET_A endothelin blockers and αvβ3 integrin receptor antagonists taught by the prior art, applicant's arguments were not found persuasive. Example 5 is generic to all blockers and antagonists, however, the prior art is specific for both the blockers and antagonists. Dosages of receptor antagonists can vary depend on the half life of the antagonist and type of antagonist such as peptide, antibody, small organic molecule, nucleic

acid or carbohydrate. Evidence has to be in the same scope as the prior art. The evidence has to show as much as the prior art.

Applicant submits that the instant invention is distinguished from Sakraida because the arts are completely different. There are very many molecules that could potentially be used to treat cardiovascular diseases. Arriving at the present invention was not simply combining a relatively small number of old elements that work similarly. Instead, it was selecting a particular combination of the treatment of cardivascular diseases out of thousands of theoretically possible combination.

It remains the Examiner's position that the instant situation is directly analogous to that which was addressed in *Sakarida and Anderson 's-black*, where an alleged invention consists of "an assembly of old elements," a court must inquire whether the claimed invention "only unites old elements with no change in their respective function," or whether the combined elements co-act with one another to produce some "new or different function" or an effect greater than the sum of the several effects taken separately." Sakraida, 425 U.S. at 60-61. The court states that if there is no such new or different function or effect, then the claimed subject matter is said to fail "the test of validity of combination patents," Sakraida, 425 U.S. at 282, and is deemed to have been obvious under 35 U.S.C 103 without the necessity of further analysis. The issue with potentially vary many molecules that could be used to treat cardiovascular diseases, the Examiner notes that the specification lists vary many molecules to combine (mix and match) to treat cardiovascular diseases.

Applicant contends that it was not obvious that the selected combination would have synergistic and other beneficial effects.

However, Applicant has not shown that the combined molecules in the prior art references have the asserted synergistic and other beneficial effects.

Applicant contented that the Office Action's position would render all combinatorial approaches to disease treatment per se unpatentable, even when a combinatorial approach leads to synergistic results.

It is the Examiner's position is that the record has to be clear that the combinatorial approach leads to synergistic results. Accordingly, it is Applicant's burden to provide evidence showing that the combinatorial approach claimed in the instant invention leads to synergistic results. The burden is thus placed on Applicant to point out how the teachings of the specification go beyond those of the prior art.

Applicant argues that there has been a long-felt but unsolved need to devise more effective treatments of cardiovascular diseases.

However, long-felt need for a generic product is not necessarily casually connected to the claimed invention directed to a specific application of the generic product. *Pentec, Inc. V. Graphic Controls Corp.*, 227 USPQ 766 (Fed. Cir. 1985).

9. No claim is allowed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B. O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

May 14, 2008

/Maher M. Haddad/
Primary Examiner,
Art Unit 1644